## REMARKS

Claims 1-88 are pending in the application. Claims 2, 17 and 29-85 are withdrawn from consideration.

Support for new claims 86-88 can be found, for instance, in original claims 10 and 20. See also the Examples. No new matter is added.

**Rejection of Claims 1, 3-16, 18, 19 and 22-28 under 35 U.S.C. §103(a)**

Claims 1, 3-16, 18, 19 and 22-28 are rejected under 35 U.S.C. §103(a) as being unpatentable over O'Hagan et al., WO 98/33487 (O'Hagan) in view of Hawkins et al., US 6,290,973 (Hawkins). This rejection and its supporting remarks are respectfully traversed.

A proper rejection under 35 U.S.C. 103 requires, *inter alia*, an explanation as to why one of ordinary skill in the art at the time the invention was made would have been motivated to make a proposed modification to the prior art to arrive at the claimed subject matter. See MPEP 706.02(j). See also Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.*, 127 S. Ct. 1727, (2007):

> The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting In re Kahn … stated that " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' "

The Examiner has asserted that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of O'Hagan with Hawkins to make an immunogenic composition comprising water, polymer microparticle, antigen adsorbed to microparticle, and various synthetic phospholipids "for the purpose of immunizing a subject to increase or enhance immunogenic activity, immune response or stimulate/enhance protection against an infectious antigen for example."

In support of her position, the Examiner has relied upon the following case law from MPEP 2144.06:

> "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a

> spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held *prima facie* obvious).

The present application, however, does not constitute a case in which *Kerkhoven* and its ilk can be relied on in support of a legal conclusion of obviousness. For example, *Kerkhoven* involved "two compositions each of which is taught by the prior art to be useful for the same purpose". Moreover, the claims required "no more than the mixing together of two conventional spray-dried detergents." 626 F.2d at 850. Similarly, *In re Crockett* involved two components, each of which was known to promote the formation of a nodular structure in cast iron, and *Ex parte Quandranti* involved mixing two compositions, each of which was known to be a herbicide.

The present facts are not analogous. Although polymer microparticles and synthetic phospholipid compounds may be broadly identified as "adjuvants," the art of record, including O'Hagan and Hawkins, do not teach or suggest that these adjuvants would be interchangeable/useful for the same purpose.

For example, O'Hagan teaches at page 2 that "[p]articulate carriers with adsorbed or entrapped antigens have been used in an attempt to elicit adequate immune responses. Such carriers present multiple copies of a selected antigen to the immune system and promote trapping and retention of antigens in local lymph nodes. The particles can be phagocytosed by macrophages and can enhance antigen presentation through cytokine release." There is no teaching or suggestion in O'Hagan or Hawkins, on the other hand, that synthetic phospholipids such as those presently claimed could be used as particulate carriers for adsorbed or entrapped antigens. Thus, O'Hagan and Hawkins clearly do *not* teach "two compositions … useful for the same purpose" and the preceding case law is not on point.

Apparently referring to MPEP 2141 (and *KSR*), has also previously stated the following (emphasis added):

> The Supreme Court further stated that: When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a ***predictable*** variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that

> it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. Id. at ___, 82 USPQ2d at 1396. When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the ***predictable*** use of prior art elements according to their established functions." Id. at ___, 82 USPQ2d at 1396.

Unlike *KSR*, which pertained to a predictable technology (i.e., automotive pedals), the present invention pertains to the chemical arts (and more particularly, the biochemical arts), which are highly unpredictable. (Such unpredictability is evidenced by the Edelman and Spickler references, discussed below.)

Indeed, the Federal Circuit, post *KSR*, has indicated that the obviousness bar is high for chemical inventions: "[t]o the extent an art is unpredictable, as chemical arts often are, *KSR*'s focus on…'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd,* 533 F.3d 1353, 1359 (Fed. Cir. 2008).

See also, *Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc.*, 520 F.3d 1358 (Fed. Cir. 2008), in which the Court affirmed the district court's denial of Mylan's motion for summary judgment of invalidity under § 103. The Court found that the ordinarily skilled artisan would have to have some reason to select among several unpredictable alternatives, which supported the conclusion that "this clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness." *Id.* at 1364.

Analogous to *Ortho-McNeil Pharmaceutical Inc., supra,* to arrive at the claimed invention, one of ordinary skill would have to have some reason to select among the myriad unpredictable alternatives known in the art. Instead, the Examiner has merely used Applicant's present specification and claims as a road map to arrive at the claimed invention.

It is further noted that a reasonable expectation of success is required to support a conclusion of obviousness. See MPEP 2143.02 and the cases cited therein, including *KSR*. Where immunological adjuvants are concerned, however, one of ordinary skill in the art would not have a reasonable expectation of success. In support of this fact, Applicant had previously presented R. Edelman, *Molecular Biotechnology*, 21(2) 2002, 129-148 (Edelman), which demonstrated that those of ordinary skill in the art would have recognized that (a) every adjuvant (including microparticle adjuvants) has a complex and often multi-factorial immunological mechanism, usually poorly understood in vivo, (b) many determinants of adjuvanticity exist and

(c) each adjuvanted vaccine is unique. Accordingly, the choice of an adjuvant frequently depends upon experimental trial and error. *Id.*

Expectations of success are even further diminished by the fact that the present invention is directed to a *combination* of adjuvants (i.e., a polymer microparticle and a synthetic phospholipid). In this regard, see, page 278 of the attached article, A.R. Spickler et al., *J Vet Intern Med* 2003;17: 273-281 (Spickler), wherein under the heading "Combined Adjuvants," the following is stated: "The result of combining adjuvants depends on the mechanism of action and toxicity of each individual component. Combinations may be better, similar to, or worse than the individual components."

In an attempt to dismiss Edelman and Spickler, the Examiner has argued that these references are not part of the 103 obviousness rejections. While this is true, it is also beside the point. Edelman and Spickler were cited by Applicant as evidence that the art of the present invention is unpredictable and thus there is no reasonable expectation of success. See MPEP 2143.02.II. ("AT LEAST SOME DEGREE OF PREDICTABILITY IS REQUIRED; APPLICANTS MAY PRESENT EVIDENCE SHOWING THERE WAS NO REASONABLE EXPECTATION OF SUCCESS").

In view of the foregoing, it is respectfully submitted that, without undue hindsight gained upon review of the present specification and claims, the presently pending claims are unobvious in view of the teachings of O'Hagan and Hawkins. See, e.g., MPEP 2142, second paragraph, *Akzo N.V. v. U.S. International Trade Commission*, 808 F.2d 1241, 1480-81, 1 U.S.P.Q.2d, 1241, 1246 (Fed. Cir. 1986), *cert. denied,* 482 U.S. 909 (1987), and *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 874, 228 U.S.P.Q. 90-99 (Fed. Cir. 1985).

Consequently, a *prima facie* case of obviousness has not been established by the Examiner. For at least these reasons, reconsideration and withdrawal of the Examiner's rejection are requested.

**Rejection of Claims 20 and 21 under 35 U.S.C. §103(a)**

Claims 20 and 21 are rejected under 35 U.S.C. §103(a) as being unpatentable over O'Hagan and Hawkins in view of Muttilainen et al., *Microbial Pathogenesis*, 1995, 18:423-436 (Muttilainen) and Cox et al., *Vaccine*, 1997, 15/3:248-256 (Cox). This rejection and its supporting remarks are respectfully traversed.

Specifically, it is alleged in the Office Action that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of O'Hagan, Hawkins, Muttilainen and Cox with a reasonable expectation of success to prepare the immunogenic compositions as claimed.

Various deficiencies in O'Hagan and Hawkins are discussed above (including the lack of articulated reasoning with some rational underpinning to support a conclusion of obviousness, lack of predictability, and lack of a reasonable expectation of success).

The Examiner cites Muttilainen as teaching a composition comprising meningitis serogroup B P1 antigen in phospholipid vesicles or liposomes and that the liposome formulation is good as an adjuvant.

With regard to Cox, the Examiner has pointed to the following statement at page 253: "The purpose of adjuvant combinations is to combine various adjuvant components to achieve the desired mix of immunological responses". This statement, however, is vague, effectively amounting to a wishful-thinking mission statement, providing no guidance or details to one of ordinary skill in the art as to which adjuvants should be selected from the myriad adjuvant materials available in the art and combined.

Even when one looks to the text of Cox itself, one is confronted with a large number of adjuvants and thus a very large number of possible two-adjuvant combinations.

Rather than contemplating the myriad adjuvant combinations that could be constructed from available adjuvant materials, Cox advocates "rational selection" from a "small number" of formulations/additives:

> Selection of the "best" adjuvant combination requires some knowledge of the chemical nature of the protective immunogen(s) and some idea of the nature of the immune response which is likely to be protective. However, even where knowledge of both these issues is minimal, rational selection of a small number of basic formulations and additives should permit selection of an effective adjuvant system....

This "small number" is presumably in reference to the small number of combinations that are described in Cox (as noted above, Cox discusses a large number of single adjuvants and thus a very large number of possible two-adjuvant combinations; hence Cox cannot be said to describe a "small number" of adjuvant combinations).

The Examiner has not demonstrated, however, that the "rational selection" taught in Cox would actually result in the claimed combination and, in fact, none of the combinations taught in Cox pertain to microparticle compositions. Rather, the discussion of adjuvant combinations on page 253 of Cox pertain generally to three types of adjuvant combinations, specifically, w/o formulations, o/w emulsions and liposome formulations, which are nothing like the solid microparticle-based adjuvant combination presently claimed.

To the extent that the Examiner believes that the above statements in Cox (1997) constitute evidence that the adjuvant art at the time of the invention was a predictable art which would have given one of ordinary skill in the art a reasonable expectation of success, this is contradicted by later-published references in the art, specifically, Edelman (2002) and Spickler (2003). As indicated above, adjuvant selection and combination is a complex and poorly understood undertaking, with successful outcomes generally being the rare result of a long, unpredictable, empirical, trial-and-error-based endeavor. See e.g., the Abstract of Edelman ("choice of an adjuvant often depends upon expensive experimental trial and error").

See also page 278 of Spickler, wherein under the heading "Combined Adjuvants," the following is stated: "Combinations may be better, similar to, or worse than the ***individual components***." (Emphasis added.) Consequently, it is noted that a *combination* of two or more adjuvants is not necessary or even desirable in many vaccines. One example of this is the *N. meningitidis* serogroup B vaccine from Novartis Vaccine and Diagnostics Inc., which is comprised five proteins with an alum adjuvant. Thus, contrary to the Examiner's assertion that one of ordinary skill in the art would be motivated to combine multiple adjuvants together, this real world example demonstrates that alum is by itself sufficient.

Citing *KSR*, the Examiner has also argued that "it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield *predictable* results." (Emphasis added.)

The Examiner's reliance on *KSR*, however, is unfounded as the invention at issue in *KSR* was in a very predictable art (i.e., automotive pedals) and there was a known problem that was

being solved. *KSR* involved addressing a known problem with "a finite number of identified, predictable solutions" *KSR*, 127 S. Ct. at 1742.

As pointed out above, adjuvant science is anything but predictable.[1] Indeed, when it comes to adjuvants, there are a near-infinite number of possible combinations that are available to the ordinarily skilled artisan, none of which is predictable. See *Ortho-McNeil v. Mylan Laboratories*, 520 F.3d 1358 (Fed. Cir. 2008). ("In sum, this clearly is not the easily traversed, small and finite number of alternatives that KSR suggested might support an inference of obviousness.")

Thus, rather than providing "some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" as required by *KSR*, the Examiner has instead, with the benefit of undue hindsight, taken random references disclosing various elements of the claimed invention and combined them together, ostensibly in the form of an obviousness rejection.

Finally, it is again noted that that one of ordinary skill in the art must have a reasonable expectation of success. Such an expectation is unfounded here for a number of reasons including, for example, the complex and poorly understood nature of adjuvant action.

For at least these reason, it is respectfully submitted that claims 20 and 21 are patentable over O'Hagan, Hawkins, Muttilainen and Cox.

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[1] In this regard, the Examiner's attention is also directed to MPEP 2143.01 III. (FACT THAT REFERENCES CAN BE COMBINED OR MODIFIED MAY NOT BE SUFFICIENT TO ESTABLISH *PRIMA FACIE* OBVIOUSNESS): "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art…."

**CONCLUSION**

Applicant submits that all pending claims are in condition for allowance, early notification of which is earnestly solicited. Should the Examiner be of the view that an interview would expedite consideration of this Amendment or of the application at large, the Examiner is requested to telephone the Applicant's attorney at (908) 518-7700 in order to resolve any outstanding issues in this case.

Respectfully submitted,

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/Keum J. Park/

Keum J. Park
Registration No. 42,059

Attorney for Applicant
Mayer & Williams PC
251 North Avenue West, 2nd Floor
Westfield, NJ 07090
Tel.: 908-518-7700
Fax: 908-518-7795

Please direct all correspondence to:

Novartis Vaccines and Diagnostics Inc.
Intellectual Property Department X-100B
P.O. Box 8097
Emeryville, CA 94662-8097